## REMARKS

### I. Status of the Claims

Claims 1-4, 6-11 and 13-17 are pending in the application, claims 5 and 12 having been canceled. Claim 11 is withdrawn pursuant to an election of species requirement, and thus claims 1-4, 6-10 and 13-17 are under consideration and stand rejected under either 35 U.S.C. §102 or §103. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

### II. Rejection Under 35 U.S.C. §102

Claims 1, 2 and 6-10 stand rejected as anticipated by Collier *et al.* The examiner takes the position that the ligand of Collier comprises an analyte antibody, and refers to column 4, lines 53 to 59 of Collier (Action, sentence spanning pages 3-4). However, applicants believe that this passage does not actually disclose that the term "analyte" refers to an antibody, thus constituting a first defect in the rejection.

Furthermore, the order of method steps in Collier is not the same as in the presently claimed methods. In Collier, the sample is first reacted with an immobilized capture reagent, which according to the examiner is the solid carrier of step b) of the present invention. Subsequently, the sample is reacted with a ligand reporter conjugate, which is alleged to be the macromolecule coupled to the at least 2 molecules of the analyte (Collier, column 9 line 62 to column 10 line 2). However, in the methods of the present invention, the sample is first incubated with the macromolecules (step a) and subsequently incubated with the solid carrier (step b). This aspect of the invention has been further clarified by amendments to claim 1, and provides a second point of distinction.

Moreover, in step c) of the presently claimed methods, the macromolecules are stained by a fluorescence dye. It is clear from the application as filed that the macromolecules of step c) are the same as the macromolecules in step a), namely, the macromolecules to each of which at least 2 molecules of the analyte to be detected are coupled (see, *e.g.*, specification page 5, lines 25 to 29). In contrast, in Collier the ligand-reporter conjugate (the alleged equivalent of the analyte-macromolecule conjugate of the present invention) is ***not*** stained by fluorescence. Rather, the method of Collier comprises an intervening step in which a nucleic acid replication composition is added so that nucleic acid amplification occurs and only ***the amplified nucleic acids are detected***, *e.g.*, by fluorescence dye staining (see column 10, lines 6 to 13 or column 22 lines 49 to 50). This is yet a third difference between the claimed methods and those of Collier.

For the foregoing reasons, Collier does not teach each element of the claimed invention, and therefore cannot be anticipatory. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

## III. Rejections Under 35 U.S.C. §103

### A. Collier in view of Reddy

Claims 3-4 and 13-17 stand rejected over Collier *et al.* in view of Reddy *et al.* Collier *et al.* is cited as above. As such, the defects outlined above persist here, and are not addressed by Reddy *et al.* Therefore, this rejection also is improper.

However, even assuming that Reddy *et al.* were able to correct the previously mentioned deficiencies of Collier *et al.*, there remains an additional problem. Reddy *et al.* is cited as further teaching incubating the sample with solid carrier to which complementary oligonucleotides, *i.e.*, capture molecules for the analyte to be detected, are coupled (see Action at page 11, first

sentence). However, while this statement might on its face be correct, it does not provide the missing teachings – marking of a macromolecule with a fluorescence dye prior to incubating with the sample – as explained below.

According to the presently claimed methods, the analyte is ***directly*** captured by binding to the capture molecule. In contrast, in Reddy *et al.* the capture molecules on the solid carrier are oligonucleotides which are complementary to oligonucleotide macromolecules to which the analyte is in turn bound. Thus, the capture in Reddy occurs by the hybridization of the two complementary oligonucleotides, thus indirectly, and ***not*** by the binding of the analyte to the capture molecule (see, *e.g.*, Reddy, column 3 line 40 to column 4 line 10). In order to clarify these differences, claim 3 has been amended. Disclosure for the direct binding of the analyte to the capture molecule can, *e.g.*, be found in the specification on page 4, lines 15 to 19.

Applicants further point out that, in Reddy, the fluorescence dye is coupled to the immunoreactant (see Reddy, column 3, lines 61 to 64). The immunoreactant is not the macromolecule of the present invention. In contrast, in the methods of the present invention, the fluorescence dye stains the macromolecule directly (claim 1) and is coupled to the macromolecule (claim 3), respectively. The examiner apparently has missed this distinction when arguing that "Reddy *et al.* also teaches that competition assay comprising fluorescence dye marked nucleic acid (*i.e.*, macromolecule) is particularly useful for detecting the presence of smaller and multiple analytes in the sample (column 3, lines 40-46)" (page 9, last sentence of the second paragraph of the office action). However, in Reddy, no nucleic acid marked with a fluorescence dye is described. In Reddy the fluorescence dye and the label, respectively, is bound to an ***immunoreactant***.

And, should the examiner continue to argue that Collier explicitly teaches that the competitive binding assays can be practiced employing alternative protocols (see Action at page 9, last paragraph; referring to column 10, lines 19-24), Collier refers only to alternative protocols regarding immobilization points, and ***not*** to detection points. Thus, the sweeping statement offered by the examiner in this regard is not supported.

In light of these shortcomings, applicants respectfully submit that even the combination of the cited art fails to provide a teaching of each element of the claimed invention. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

**B. Reddy in view of Collier**

Claims 1-4, 6-10 and 13-17 stand rejected over Reddy *et al.* in view of Collier *et al.*, both of which are described above. According to the examiner, the only teaching missing from Reddy *et al.* that is found in claims 1 and 3 is the attachment of two, not one, analyte molecules to the macromolecule. This deficiency is said to be corrected by Collier *et al.* Applicants again traverse.

As already explained, Reddy *et al.* certainly lacks more than the suggested two-analyte teaching. To reiterate, according to the presently claimed methods, the analyte is ***directly*** captured by binding to the capture molecule. In contrast, in Reddy *et al.* the capture molecules on the solid carrier are oligonucleotides which are complementary to oligonucleotide macromolecules to which the analyte is in turn bound. Thus, the capture in Reddy occurs by the hybridization of the two complementary oligonucleotides, thus indirectly, and ***not*** by the binding of the analyte to the capture molecule (see, *e.g.*, Reddy, column 3 line 40 to column 4 line 10). In order to clarify these differences, claim 3 has been amended. Disclosure for the direct binding

of the analyte to the capture molecule can, *e.g.*, be found in the specification on page 4, lines 15 to 19. Also, as discussed above, Reddy's fluorescence dye is coupled to the immunoreactant (see Reddy, column 3, lines 61 to 64). The immunoreactant is not the macromolecule of the present invention. In contrast, in the methods of the present invention, the fluorescence dye stains the macromolecule directly (claim 1) and is coupled to the macromolecule (claim 3), respectively. The examiner apparently has missed this distinction when arguing that "Reddy *et al.* also teaches that competition assay comprising fluorescence dye marked nucleic acid (*i.e.*, macromolecule) is particularly useful for detecting the presence of smaller and multiple analytes in the sample (column 3, lines 40-46)" (page 9, last sentence of the second paragraph of the office action). However, in Reddy, no nucleic acid marked with a fluorescence dye is described. In Reddy the fluorescence dye and the label, respectively, is bound to an ***immunoreactant***.

In light of these distinctions, it would make ***no sense*** to select Reddy as the primary reference given the distinct differences with the presently claimed methods. Moreover, in order to engineer this feature out of Reddy, for example, by substituting the capture molecule of Collier, one turns Reddy upside-down. Obviousness must take into account the teachings of the prior art ***as a whole***. MPEP §2141.02 states that "In determining the differences between the prior art and the claims, the question under 35 U.S.C. §103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious," citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983) (emphasis in original). Following this guidance, if one looks at Reddy, one would not change the capture system so completely as to arrive at the teachings of Collier.

Thus, for the reasons already given, the claims remain patentable over the same two references, when taken in the opposite order. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

## IV. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. The examiner is invited to contact the undersigned attorney at (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

Steven L. Highlander
Reg. No. 37,642
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 536-3184

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